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Adverse Effects Associated With High-Dose Recombinant Human Bone Morphogenetic Protein-2 Use in Anterior Cervical Spine Fusion

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Study Design. A retrospective review of patients who underwent an anterior cervical fusion using recombinant human bone morphogenetic protein (rhBMP)-2 with an absorbable collagen sponge (INFUSE®; Medtronic Sofamor Danek, Minneapolis, MN).

Objective. To ascertain the complication rate after the use of high-dose INFUSE® in anterior cervical fusions.

Summary of Background Data. The rhBMP-2 has been primarily investigated in lumbar spine fusions, where it has significantly enhanced the fusion rate and decreased the length of surgery, blood loss, and hospital stay.

Methods. We present 151 patients who underwent either an anterior cervical discectomy and fusion (n = 138) or anterior cervical vertebrectomy and fusion (n = 13) augmented with high-dose INFUSE® between July 2003 and March 2004. The rhBMP-2 (up to 2.1 mg/level) was used in the anterior cervical discectomy and fusions.

Results. A total of 35 (23.2%) patients had complications after the use of high-dose INFUSE® in the cervical spine. There were 15 patients diagnosed with a hematoma, including 11 on postoperative day 4 or 5, of whom 8 were surgically evacuated. Thirteen individuals had either a prolonged hospital stay (>48 hours) or hospital readmission because of swallowing/breathing difficulties or dramatic swelling without hematoma.

Conclusions. A significant rate of complications resulted after the use of a high dose of INFUSE® in anterior cervical fusions. We hypothesize that in the cervical area, the putative inflammatory effect that contributes to the effectiveness of INFUSE® in inducing fusion may spread to adjacent critical structures and lead to increased postoperative morbidity. A thorough investigation is warranted to determine the optimal dose of rhBMP-2 that will promote cervical fusion and minimize complications.

Key words: rhBMP-2, INFUSE®, anterior cervical discectomy and fusion, cervical vertebrectomy, cervical fusion, complications. **Spine 2006;31:542–547**

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Anterior cervical discectomy and fusion (ACDF) is a widely practiced surgical procedure for the treatment of cervical spondylosis and disc herniation. This intervention initially used autogenous bone, most commonly from the iliac crest, as the interbody graft. The morbidity resulting from graft-site harvest may affect up to 30% of patients, and include neurologic damage, chronic pain, and risk of infection.[1,2] This staggering percentage led to the use of bone graft substitutes, including homologous bone and a family of growth factors known as bone morphogenetic proteins (BMPs).

Both recombinant human bone morphogenetic protein-2 and -7 (rhBMP-2 and OP-1) have been used in the clinical setting in place of autogenous bone graft, and for bone augmentation and repair.[3,4] The rhBMP-2 has been capable of osteoinduction, specifically, the ability to induce *de novo* bone formation at a nonbony site.[5] It has been studied extensively in lumbar spine fusions using animal models[6–12] and in human beings.[1,13–17] Lumbar fusion using rhBMP-2 has reduced the operating time, blood loss during surgery, and hospital stay, and has reflected a higher fusion rate at 24 months compared to lumbar fusion using autogenous bone.

The success of a fusion using rhBMP-2 is dependent on a triad of factors, including site, dose, and carrier specificity.[18] The INFUSE® Bone Graft (Medtronic Sofamor Danek, Minneapolis, MN) combines rhBMP-2 with an absorbable collagen sponge to induce osteogenesis.[19] The Food and Drug Administration has approved the use of a type-I collagen sponge enhanced with rhBMP-2 in combination with a tapered, threaded fusion cage (LT-CAGE®; Medtronic Sofamor Danek) for the treatment of lumbar degenerative disc disease.[20]

Although less attention has been focused on the use of rhBMP-2 in anterior cervical spine fusions, both animal[21–23] and human[24] studies have shown favorable outcomes. The primary feature was the ability of rhBMP-2 to enhance significantly the rate of fusion without associated adverse effects. We reviewed the cases of 151 patients who underwent either an ACDF or anterior cervical vertebrectomy and fusion using a higher dose of INFUSE® than had been previously studied, over an 8-month period.

Materials and Methods

Patient Data. A total of 151 patients underwent either an ACDF (n = 138) or vertebrectomy (n = 13) using INFUSE®

Bone Graft between July 2003 and March 2004. There were 62 men (41.0%) and 89 women (59.0%) included in the study. The ages ranged between 28 and 80 years, with a mean age of 49.9 years. All individuals had pursued conservative treatment before surgical intervention. Preoperative imaging studies revealed spondylosis in 112 (74.2%) patients and a disc herniation in 39 (25.8%). The following preoperative symptoms were reported: neck pain in 148 (98.0%), arm pain in 136 (90.0%), arm numbness in 106 (70.2%), and arm weakness in 84 patients (55.6%). A total of 30 (20.0%) patients had undergone previous cervical surgical procedures, including an anterior discectomy in 29 and an anterior vertebrectomy in 1. Numerous behavioral or medical conditions associated with an increased risk during anterior cervical surgery were documented: cigarette smoking in 59 patients (39.1%), hypertension in 53 (35.1%), diabetes mellitus in 15 (9.9%), rheumatoid arthritis in 2 (1.3%), Coumadin (Bristol-Myers Squibb Co., Princeton, NJ) use in 2 (1.3%), and 1 patient each of the following—prior radiation to the cervical region, factor V Leiden mutation (clotting disorder), hemochromatosis, von Willebrand disorder, acetylcholinesterase inhibitor deficiency, or fish allergy in 1 patient each.

Graft and rhBMP-2. Of the 138 patients who underwent an ACDF, 135 received a resorbable poly(D,L-lactic acid) cage (HYDROSORB 228; Medtronic Sofamor Danek), with a collagen carrier enhanced with rhBMP-2 within the graft, while 3 patients received the homologous bone graft (CORNERSTONE®; Medtronic Sofamor Danek), with the rhRMP-2-laden collagen carrier inserted in the graft. A titanium mesh cage (PYRAMESH 228 ; Medtronic Sofamor Danek) was used in all 13 individuals who underwent an anterior cervical vertebrectomy and fusion. A total of up to 2.1 mg of rhBMP-2 per level in the ACDFs was reconstituted as a 1.4 mL solution and soaked in a sponge measuring 2.5 × 5.0 cm. The total surface area of the sponge was 12.5 cm^2 (0.112 mL solution/cm^2). The rhBMP-2 was placed within the construct in the ACDFs, with a higher amount used in the anterior cervical vertebrectomy and fusions.

Surgical Technique

ACDF and Anterior Cervical Vertebrectomy and Fusion. A right-sided incision was made in the cervical area. An intraoperative lateral cervical spine radiograph was used to confirm the appropriate level or levels. The modified Smith-Robinson technique was subsequently performed. At completion of the decompression in the ACDFs, cartilaginous endplates were decorticated followed by wound irrigation with copious amounts of bacitracin-containing solution. The cage or graft was selected, filled with INFUSE®, tapped into the disc space, and countersunk 1 mm. Additional INFUSE® was frequently placed lateral and anterior to the graft (under the plate) within the disc space. An anterior cervical plate (ZEPHYR 228; Medtronic Sofamor Danek) was then placed. An intraoperative radiograph confirmed proper alignment and fixation of the bone graft and plate. Vocal cord monitoring was used throughout the surgical procedure.

At completion of the decompression in the anterior cervical vertebrectomy and fusions, the foramina were opened bilaterally. A PYRAMESH 228 cage was appropriately sized, cut, and contoured for the vertebrectomy defect. The cage was packed with a combination of local bone and INFUSE®, and impacted into the defect. Additional INFUSE® was packed anterior and lateral to the cage. Drill sites were formed bilaterally in the vertebral bodies, and a cervical plate was subsequently placed with 13-mm screws. An intraoperative lateral cervical radiograph showed appropriate positioning of the plate and cage.

Table 1. A Total of 151 Patients Underwent Either an ACDF or an Anterior Cervical Vertebrectomy and Fusion Using INFUSE®

Procedure	No. (%)
ACDF (n = 138)	
1-Level	61 (44.2)
2-Level adjacent	68 (49.3)
3-Level adjacent	6 (4.3)
2-Level noncontiguous	3 (2.2)
Anterior vertebrectomy and fusion (n = 13)	
1-Level	4 (30.8)
2-Level	5 (38.5)
3-Level	3 (23.1)
4-Level	1 (7.7)

■ Results

Surgical Outcomes

A total of 138 patients underwent either a 1, 2, or 3-level adjacent ACDF, or a noncontiguous 2-level ACDF (Table 1). There were 13 individuals who underwent a 1, 2, 3, or 4-level anterior vertebrectomy. The anterior approach solely was used in 149 patients, while 3 patients underwent a 2 in 1 procedure, consisting of both anterior and posterior cervical approaches on the same day. A drain was surgically placed in 35 (25.4%) of 138 patients who underwent an ACDF and in 8 (61.5%) of 13 patients who underwent an anterior cervical vertebrectomy and fusion. The majority of individuals were released from the hospital within 24 hours of their surgery.

Complications

Hematoma. There were 15 (9.9%) patients diagnosed with a hematoma after undergoing anterior cervical surgery using INFUSE® (Table 2). Eleven patients were diagnosed with a hematoma on the fourth or fifth postoperative day, consisting of 7 and 4 patients, respectively. There were 8 patients who underwent surgical evacuation of the hematoma (Figures 1, 2). Of these individuals, 4 had undergone a 2-level adjacent ACDF, 2 a 1-level vertebrectomy, and 2 a 2-level vertebrectomy. There was 1 patient who had previously undergone a 1-level ACDF, while 3 previously underwent a 2-level ACDF. Of the 7

Table 2. Presence of a Hematoma After Anterior Cervical Spine Fusion

	Postoperative Day (Previous Anterior Cervical Fusion)	
Procedure	Less than Day 4	Days 4 or 5
1-Level ACDF	1 (1)	4 (1)
2-Level ACDF	0 (0)	5 (1)
1-Level vertebrectomy	1 (1)	1 (1)
2-Level vertebrectomy	1 (0)	1 (1)

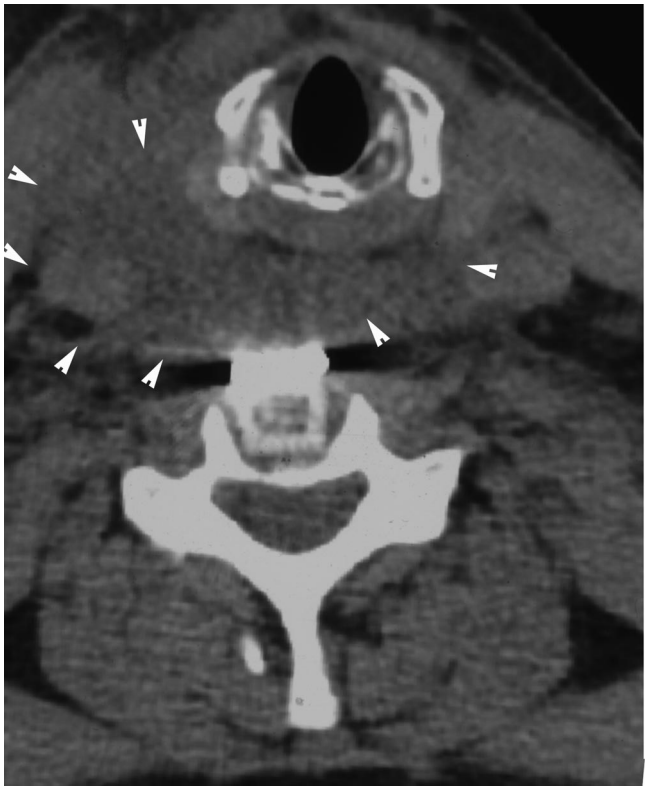

Figure 1. Cervical computerized tomography indicates an extensive postoperative hematoma (outlined by arrowheads) in the retropharyngeal space that displaces the trachea anteriorly at the level of the allograft INFUSE® construct. The hematoma is predominantly on the right side, and is 2.0-cm thick, 5.5-cm wide, and 8.5-cm long. The horizontal black radiolucency posterior to the hematoma represents a plate artifact. The hematoma was evacuated.

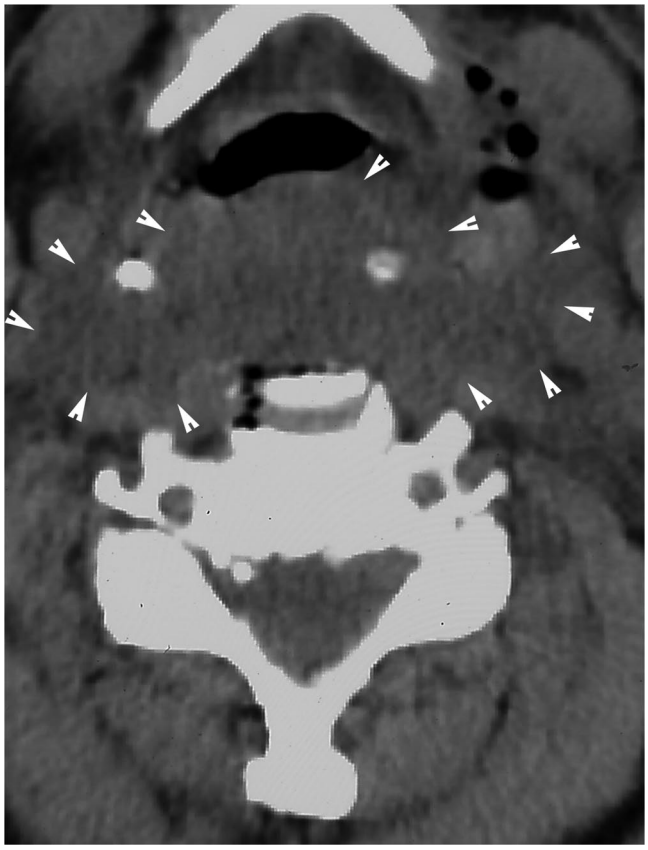

Figure 2. Gadolinium-enhanced cervical computerized tomography that indicates extensive symmetrical hemorrhage (arrowheads) located anterior to the allograft INFUSE® construct. The hematoma encircles the carotid arteries (circular enhancing structures within the hematoma), causing marked anterior displacement of the trachea and esophagus. The hematoma is 4.0-cm thick, 7.0-cm wide, and 12.0-cm long. The hematoma was evacuated.

patients diagnosed with a hematoma who did not undergo evacuation of the hematoma, 4 had undergone a 1-level ACDF, 2 a 2-level adjacent ACDF, and 1 a 2-level noncontiguous ACDF. There was 1 patient who had previously undergone a 2-level ACDF and another who previously underwent a 1-level ACDF. A drain was placed in 7 patients (46.7%) who had a hematoma at the index procedure.

Prolonged Hospital Stay (>48 hours) or Readmission for Swallowing/Breathing Difficulties Without Hematoma or Reoperation. There were 13 (8.6%) patients who had either a prolonged hospital stay (>48 hours) (n = 5) or readmission to the hospital (n = 8) after undergoing anterior cervical surgery using INFUSE® (Table 3). Their complaints included dysphagia, respiratory difficulties, and incisional swelling. There were 6 patients who were readmitted on either postoperative day 3 or 4. Eight individuals had undergone a 2-level ACDF, 3 a 1-level ACDF, 1 a 2-level vertebrectomy, and 2 a 1-level vertebrectomy. Only 1 patient in this category had undergone previous anterior cervical surgery. There were 3 (23.1%) patients who underwent placement of a drain at the index procedure.

Additional Complications. There were 10 patients (6.6%) who had a myriad of additional complications after anterior cervical surgery using INFUSE®, including syndrome of inappropriate secretion of antidiuretic hormone (SIADH), collapse of the upper lobe of the right lung, Horner syndrome, vocal cord palsy, superficial

Table 3. Prolonged Hospital Stay (>48 hs) or Readmission for Swallowing/Respiratory Difficulties or Incisional Swelling Without Evidence of Hematoma

Patient	Procedure	Prolonged Stay or Readmission (POD)	Previous Anterior Cervical Fusion
1	1-Level ACDF	Prolonged stay	1-Level ACDF
2	2-Level ACDF	Prolonged stay	
3	2-Level ACDF	Prolonged stay	
4	2-Level ACDF	Prolonged stay	
5	2-Level vertebrectomy	Prolonged stay	
6	1-Level ACDF	Readmission (2)	
7	1-Level ACDF	Readmission (4)	
8	2-Level ACDF	Readmission (3)	
9	2-Level ACDF	Readmission (3)	
10	2-Level ACDF	Readmission (3)	
11	2-Level ACDF	Readmission (3)	
12	2-Level ACDF	Readmission (5)	
13	1-Level vertebrectomy	Readmission (4)	

POD indicates postoperative day.

Table 4. Complications After Anterior Cervical Spine Fusion Besides Hematoma or Swallowing/ Respiratory Difficulties

Patient	Complication	Procedure	Previous Anterior Cervical Fusion
1	SIADH	2-Level ACDF	1-Level ACDF
2	Collapse of right upper lobe of lung	3-Level vertebrectomy (2 in 1)	
3	Horner syndrome	1-Level ACDF	1-Level ACDF
4	Horner syndrome	1-Level ACDF	
5	Vocal cord palsy	2-Level ACDF	
6	Vocal cord palsy	1-Level ACDF	1-Level ACDF
7	Superficial stitch abscess	1-Level ACDF	
8	Implant dislodgement	2-Level vertebrectomy	
9	Implant dislodgement	1-Level ACDF	
10	Graft resorption	1-Level ACDF	1-Level ACDF

stitch abscess, implant dislodgement, and graft resorption (Table 4).

■ Discussion

The rhBMP-2 has been investigated in lumbar spinal fusions in several prospective randomized human clinical trials since 1997.[1,13–17] In these previous studies, patients in both the investigational groups who received rhBMP-2 on an absorbable collagen sponge (INFUSE® Bone Graft) and those in the control groups who received autogenous iliac crest bone graft had an improvement in clinical outcome, however, mean operating time, blood loss, and hospital stay were less in the rhBMP-2 groups.[1,13–15,17] Furthermore, the investigational patients had a higher fusion rate at 24 months.[1,13–17] Based on clinical data, the Food and Drug Administration has advised that rhBMP-2 be approved as the first complete bone graft substitute for spinal fusion.[5,25]

Although the experience with rhBMP-2 in anterior cervical fusion is far more limited, both animal and human pilot studies have been performed. Takahashi *et al*[22] studied the effect of 0, 5, and 50 μg of rhBMP-2 added to a porous hydroxyapatite graft in goats that underwent a 3-level anterior discectomy. A solid fusion was noted in goats that received 50 μg of rhBMP-2. Zdeblick *et al*[23] studied the effect of a cervical intervertebral device filled with either autogenous bone graft or rhBMP-2 in 21 Alpine goats that underwent a 3-level ACDF. They reported a higher arthrodesis rate and accelerated bone formation in the group treated with a rhBMP-2-filled BAK device compared to the groups that underwent placement of an autogenous bone-filled BAK device that was either a standard titanium device or hydroxyapatite-coated.

Baskin *et al*[24] conducted a human pilot study in anterior cervical discectomy and interbody fusion. The investigational group received a fibular allograft containing a rhBMP-2-laden collagen carrier followed by placement of an anterior cervical plate. The control group received a fibular allograft filled with cancellous iliac crest autograft followed by plating. The 33 patients underwent either a 1-level or 2-level arthrodesis. Both groups had significant improvement in both neck and arm pain, as well as a 100% fusion rate at 6 months. The patients in the rhBMP-2 group avoided the pain, scarring, and morbidity associated with harvesting bone from the iliac crest.

Important differences exist in both rhBMP-2 dose and delivery mechanism between the technique used in the study by Baskin *et al*[24] as compared to our cases. Baskin *et al*[24] used 0.4 mL (0.6 mg) of reconstituted rhBMP-2 solution distributed on a 1.5 × 2.5-cm sponge within the bone graft per level of the fusion. In our study, up to 2.1 mg of rhBMP-2 per level was reconstituted as a 1.4 mL solution and soaked in a sponge measuring 2.5 × 5.0 cm. One sponge per level was used in the ACDFs that was placed within and occasionally on the lateral surface of a resorbable cage. In this respect, the surface area of the sponge in the study by Baskin *et al*[24] was 3.75 cm^2 (0.107 mL solution/cm^2), whereas ours was 12.5 cm^2 (0.112 mL solution/cm^2) per level. The concentration of Baskin *et al*'s and our rhBMP-2 mixture was nearly identical. Also, an even higher amount of rhBMP-2 was used in our study during the anterior vertebrectomies and fusions compared to the ACDFs. The relevance, if any, of using a resorbable cage for the ACDFs in our study *versus* a Smith-Robinson style interbody allograft as used in the study by Baskin *et al*[24] is unknown.

The anterior surgical approach for the treatment of neural compression by either a disc herniation or osteophyte has gained in popularity and is associated with a low postoperative morbidity (approximately 3%).[26] A compilation of reports representing more than 700 cases of anterior cervical fusion showed that the most frequent postoperative complications included dysphagia, hoarseness, and hematomas.[27] The incidence of dysphagia after ACDF has varied between 11% and 67%.[28] Smith-Hammond *et al*[28] reported a significant increase in swallowing complaints after anterior cervical fusion, with the majority of patients recovering within 2 months. Radiologic evidence of dysphagia was significantly associated with an age of patients older than 60 years, although was not related to surgical level, instrumentation, or operating time. Hoarseness has been reported as being transient in 8% of patients and permanent in 2%.[29]

Tew and Mayfield[30] presented the incidence of complications of 500 surgical procedures with the anterior cervical approach as: recurrent laryngeal palsy, 4 cases, including 1 permanent (0.8%), and 1 case (0.2%) each of hematoma, infection, and Horner syndrome. Although the reported incidence of recurrent laryngeal nerve palsy is approximately 1%, it has been reported as high as 11%.[31] Other complications may include graft extrusion or resorption,[32] a dural tear and cerebrospinal fluid leak,[25] or a superficial or deep wound infection.[33,34]

In this series, a total of 35 (23.2%) patients had complications after undergoing an anterior cervical fusion using INFUSE®. Although the lack of a prospective design and concurrent control group is an obvious shortcoming of the study, this rate of complications is markedly higher than either historical literature controls or our anecdotal clinical experience. The complications seen in 28 of these patients are most likely related to the use of high-dose INFUSE®. Specifically, hematomas that occurred both more frequently and after the immediate postoperative period, extensive swallowing and respiratory difficulties, and dramatic neck swelling beyond the area of the incision, represented a different clinical presentation than our prior experience. The remaining complications do not appear to be related to the use of INFUSE®, including the SIADH, collapse of a lung, Horner syndrome, hoarseness/vocal cord palsy, superficial stitch abscess, implant dislodgement, and graft resorption.

There were 15 patients who had a hematoma after undergoing an anterior cervical fusion augmented with high-dose INFUSE®. Eleven individuals were diagnosed with the hematoma on postoperative days 4 or 5. There were 11 cases that were ACDFs, and 4 were anterior vertebrectomies and fusions, reflecting 7.9% of the total ACDFs and 30.8% of the total vertebrectomies. This finding may be a result of the higher amount of INFUSE® placed within and beside the cage during the vertebrectomy procedure. A prior ACDF may also serve as a potential risk factor. There were 6 individuals diagnosed with a hematoma who had previously undergone an anterior cervical fusion, including 2 with a 1-level ACDF and 4 with a 2-level ACDF. Of the 4 patients who underwent a vertebrectomy and fusion, and had a hematoma develop after surgery, 3 had previously undergone a 2-level ACDF. The risk of complications may be considerably increased in patients who undergo an anterior cervical vertebrectomy and fusion, and who have had a previous anterior cervical fusion.

A total of 13 patients had complications other than a hematoma after the anterior cervical fusion, including swallowing/respiratory difficulties and incisional swelling. These patients either remained in the hospital for longer than 48 hours after their cervical surgery or were readmitted to the hospital. There were 11 individuals who had undergone an ACDF, while 2 underwent an anterior cervical vertebrectomy and fusion. Compared to the hematoma group, in which 6 of the 15 individuals had undergone a previous anterior cervical fusion, only 1 patient in the nonhematoma group had previously undergone an anterior cervical fusion, consisting of a 1-level ACDF. In addition, only 2 patients in the nonhematoma group underwent an anterior cervical vertebrectomy and fusion compared to 4 individuals in the hematoma group.

The data suggest that the rate of complications seen in this series may be related to the dose of INFUSE® used. Baskin *et al*[24] used a rhBMP-2 dose of 0.6 mg/level without reported complications, as opposed to the dose of up to 2.1 mg/level of rhBMP-2 for the ACDF procedures in this study. Furthermore, a higher percentage of complications occurred after anterior cervical vertebrectomy and fusion, in which an even larger amount of rhBMP-2 was used. It is also possible that the complication rate could be related to surgical technique, the use of a resorbable implant, or placement of INFUSE® outside of the implant.

Regardless of graft material, the risk of a hematoma developing may be increased with extensive surgical exposure, such as associated with a vertebrectomy compared to an ACDF. Furthermore, previous anterior cervical spine surgery may also increase the risk of hemorrhage because hemostasis is more difficult to attain within the vicinity of a scar. However, the hematomas associated with high-dose INFUSE® differ from those resulting as a complication after anterior cervical fusion without the use of INFUSE® in that the former are encountered despite the use of a drain, in a higher frequency, and at a later date (specifically, postoperative day 4 or 5). Almost half the patients who had a postoperative hematoma had a drain placed as a component of their surgical procedure. Cervical computerized tomography may prove beneficial after surgery to differentiate between hematoma and edema, yet may be deferred in cases when a patient's compromised condition necessitates immediate cervical exploration.

The present review represents the largest reported series treated with an anterior cervical fusion using INFUSE®. The high complication rate is alarming and warrants intense scrutiny. The favorable effect of INFUSE®, specifically early osteogenesis, may include an inflammatory reaction that can dissipate to critical structures within the cervical area. Although a myriad of complications, including dysphagia, hoarseness, and hematoma, have been associated with anterior cervical fusion before the use of INFUSE®, the rate of complications in this series implies a causal relationship to the use, or potentially misuse, of INFUSE®. This study emphasizes the risk associated with application of new technologies in areas in which extensive clinical experience is not available. Further investigation is necessary to determine the optimal surgical technique and dose of rhBMP-2 that will effectively enhance anterior cervical fusion, but minimize complications.

■ Key Points

- The rhBMP-2 promotes bone formation and enhances the rate of spinal fusion.
- This study raises the possibility that the use of up to 3.5 times the previously published dose of INFUSE® may lead to postoperative morbidity, such as hematomas, dysphagia, and excessive edema, after anterior cervical fusion.
- Determination of the optimal dose of rhBMP-2 is warranted to decrease the likelihood of complications after anterior cervical fusion.

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